## REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims. Please cancel claims 19-31, 23-40, 47-49, 51, 53, 55-57, 59, 61, and 63 without prejudice or disclaimer. Applicants reserve the right to file one or more continuation or divisional applications to claim cancelled and non-elected subject matter.

Specifically, claim 56 was cancelled since it was a duplicate of claim 54.

Applicants have amended claim 22 to incorporate the limitations of claim 48. Claim 50 has been amended to correct an obvious typographical error. No new matter has been added in these amendments.

Applicants respectfully request reconsideration and withdrawal of the objection to the claims and pending rejections under 35 U.S.C. §§ 103(a) and 112, first paragraph.

### Objection to the Claims

The Examiner objects to claims drawn to non-elected inventions as having incorrect claim status identifiers. Applicants have amended the claim status identifiers accordingly, thereby rendering this objection moot.

### Rejection under 35 USC § 112, First Paragraph

The Examiner rejects claims 22, 50, 52, 54, 56, 58, 60, 62 and 64 under 35 USC § 112, first paragraph, for an alleged lack of enablement. Specifically, the Examiner contends that while the specification is enabling for certain phosphodiesterase inhibitors, the specification does not reasonably provide enablement for a method of increasing glucose uptake by skeletal muscle comprising administration of any phosphodiesterase antagonist. Applicants respectfully disagree. However, solely to expedite prosecution, Applicants have amended claim 22 to recite the phosphodiesterase inhibitors specifically acknowledged as enabled by the Examiner. The recited phosphodiesterase inhibitors were originally claimed in claim 48. Thus, this amendment does not comprise new matter. In view of the foregoing, Applicants respectfully request removal of this rejection.

**Rejection under 35 USC § 103(a)**

The Examiner rejects claims 22, 50, 52, 54, 56, 58, 60, 62 and 64 under 35 USC § 103(a) as allegedly obvious over Yamasaki et al. (EP 1020452) in view of Lautt (*Can. J. Physiol. Pharmacol.*, 1999) and rejects claim 48 over Yamasaki et al. in view of Lautt and Nakaya et al. (*Diabetes Obes. Metab.*, 1999). Since Applicants amended claim 22 to incorporate claim 48, the rejection over just Yamasaki et al. and Lautt is moot. The rejection of claim 48 pertains to the currently amended claim 22 and all its dependent claims. Applicants respectfully traverse the rejection.

To make a *prima facie* case of obviousness, the teachings of the prior art should have suggested the claimed subject matter to the person of ordinary skill in the art, and all the claim limitations must be taught or suggested in the references cited by the Examiner. *In re Kotzab*, 217 F.3d 1365, 1370 (Fed. Cir. 2000). As articulated by the Supreme Court, a combination is obvious if it is no more than the predictable use of known elements according to their established functions; and there was a reason to combine the known elements. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. __, 127 S. Ct. 1727 (2007). To make a *prima facie* case of obviousness, "it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." *Id.* A dependent claim is not obvious if the claim from which it depends is not obvious. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988).

To summarize, the Examiner cites:

1. Yamasaki et al. for teaching benzimidazole derivatives as having blood sugar level-depressing activity or PDE5-inhibiting activity;
2. Lautt for teaching glucose uptake in response to insulin is largely dependent on skeletal muscle; and
3. Nakaya et al. for teaching a phosphodiesterase III inhibitor increase insulin sensitivity.

Applicants respectfully assert that the Examiner has not established that the prior art teaches or suggests all of the claim elements. The instant independent claim 22 recites a method of increasing glucose uptake. As the Examiner has stated, Lautt teaches that glucose uptake in response to insulin is largely dependent on skeletal muscle. However, the Examiner has not

provided any art that establishes that the recited phosphodiesterase antagonists increase glucose uptake. The cited art does not establish that any phosphodiesterase antagonist increases glucose uptake. Applicants assert that glucose uptake and increased insulin sensitivity/blood sugar level depressing activity are **not** the same. Thereby, the Examiner has not established that the prior art teaches or suggests all of the elements.

The Examiner asserts that Nakaya et al. demonstrates that cilostazol improves insulin sensitivity, thus one would expect with a reasonable degree of success that cilostazol could be employed in order to increase glucose uptake by skeletal muscle. The Examiner's reasoning is an unsupported, conclusory statement. The Examiner has not provided any evidence that administration of a compound that increases insulin sensitivity would necessarily increase glucose uptake by skeletal muscle. Without art teaching or suggesting that increased glucose uptake necessarily follows increased insulin sensitivity, then the Examiner has not established a *prima facie* case of obviousness.

**Further Discussion**

Yamasaki teaches (in Example 86 and at paragraph 391) that the novel benzimidazole derivative taught has blood sugar level-depressing activity, or PDE5 inhibiting activity. Yamasaki however does not teach that the uptake of glucose in skeletal muscle, or the uptake of glucose at all, rather only teaches blood sugar level-depressing activity. The increase in levels of blood sugar offered by the compound in Yamasaki could be due to a variety of mechanisms. The Examiner combines Yamasaki with Lautt, stating that it teaches that glucose uptake in response to insulin is largely dependent on uptake in skeletal muscle. Applicants respectfully submit that nowhere does Yamasaki teach that the reduction in blood glucose has anything to do with insulin response, or an increased insulin response when the Yamasaki benzimidazole derivate is administered. As the Examiner knows, a finding of obviousness requires that the pieces of prior art when combined teach all of the elements in the claim. Yamasaki does not teach that the compound in Yamasaki provides any kind of modification in insulin response but rather only teaches that there is a decrease in blood sugar levels when the compound is administered. Thus

there is a gap in the knowledge in the prior art; the two prior art references cannot be combined to teach that a compound with PDE5 inhibiting activity and blood sugar level-depressing activity can be used to increase the uptake of blood sugar in skeletal muscle.

Note also that at paragraph 391, the novel benzimidazole derivatives of Yamasaki are taught to have blood sugar level-depressing activity or PDE5 inhibiting activity. The only evidence in Yamasaki that the compound has PDE5 inhibitory activity is Example 86, which shows that the compound has blood sugar and blood triglyceride lowering activity. There is no discussion or suggestion that this activity is a result of a response to insulin or uptake in skeletal muscle or even the uptake of glucose, rather it only teaches the decrease in serum glucose levels.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 USC § 103(a).

## SUMMARY

In view of the foregoing, Applicants believe that the claims are in condition for allowance and such action is respectfully requested. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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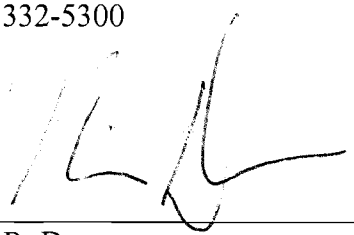

Date: July 24, 2008

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